24. (New) The ligand-bonded complex according to claim 7, including a drug for at least one of therapeutic and prophylactic treatments and diagnosis in the microparticle.

25. (New) The ligand-bonded complex according to claim 8, including a drug for at least one of therapeutic and prophylactic treatments and diagnosis in the microparticle.

26. (New) The ligand-bonded complex according to claim 9, including a drug for at least one of therapeutic and prophylactic treatments and diagnosis in the microparticle.

REMARKS

Upon entry of the instant amendment, claim 3 will be canceled without prejudice or disclaimer of the subject matter recited therein, claim 9 will be amended, and claims 19-26 will be added, whereby claims 1-26 will be pending. Claim 1 is the sole independent claim.

Applicants note that support for newly-added claims 19-26 is present throughout Applicants' originally filed disclosure, including page 8, line 17 et seq.

Applicants note that two Office Actions and one personal interview have been already been made in the present application. Applicants therefore request a careful examination of the application and a thorough review of the application based upon its entire file history, including the present response. If for any reasons the Examiner deems that the application is not in condition for allowance, the Examiner is respectfully requested to contact the undersigned by telephone to discuss any outstanding issues in order that this application can be advanced to issue without undue burden and without further expense for responding to an additional Office Action.

Reconsideration and allowance of the application are respectfully requested.

Response To Rejection Under 35 U.S.C. 112, Second Paragraph

Claims 3 and 9 are rejected under 35 U.S.C. 112, second paragraph, because it is asserted that the claims are indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

In this ground of rejection, it is asserted that in claim 3, line 2, "sufficient" is vague as there is no definition or guidance provided for the term in the specification.

In response, Applicants respectfully submit that "sufficient ligand for reaction with the non-free target" is readily understandable to one having ordinary skill in the art following Applicants' originally filed disclosure. For example, the Examiner's attention is directed to Applicants' specification, at page 2, under the section entitled "Disclosure of Invention", wherein it is disclosed that:

> In order to solve the aforementioned problem, the inventors of the present invention conducted researches on the relationship between soluble target substances such as a free antigen and ligands such as an antibody. Surprisingly, it was found that a ligand-bonded complex, to which plural numbers of a ligand having a low affinity to a target substance were bonded, had a high reactivity to a non-free target such as a cancer cell even in the presence of a free target substance. The present invention was achieved on the basis of these findings.
>
> The present invention thus provides a ligand-bonded complex which does not substantially bind to a free target substance such as a free antigen, but can specifically react with a non-free target such as a cancer cell. More specifically, the present invention provides a ligand-bonded complex in which a ligand having affinity for a target is bonded directly or indirectly to a microparticle, wherein the affinity of the ligand is sufficient to allow substantially specific binding of the ligand-bonded complex to a non-free target even in the presence of a free target; the aforementioned complex wherein two or more of a single kind of a ligand having substantially the same affinity are bonded to one microparticle; **and the aforementioned complex wherein an amount of the ligand is sufficient for reaction of the ligand with the non-free target**. (Emphasis added)

Moreover, throughout the specification guidance is provided for practicing Applicants' invention. Thus, as the Examiner realizes in view of the fact that an enablement rejection has not been made in the Office Action, Applicants' invention is enabled for the ligand having an affinity for the target substance so that the affinity allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target.

Applicants respectfully submit that this aspect of their invention which is included in claim 1 is clearly and completely defined. Therefore, claim 3 is being canceled without prejudice to the canceled subject matter being included in the invention recited in independent claim 1.

Still further, the rejection asserts that, in claim 9, "a marker molecule" is vague and indefinite.

In response, to advance prosecution of the application, and without expressing any agreement or acquiescence with the rejection, Applicants have deleted "a marker molecule" from the claim. Accordingly, this ground of rejection has been rendered moot.

For the reasons indication above, this ground of rejection should be withdrawn.

Response To Rejections Based Upon Prior Art

(a) Claims 1, 4-6, and 8-15 are rejected under 35 U.S.C. 102(b) as being anticipated by U.S. Patent No. 5,527,528 to Allen et al. ("Allen"). The rejection asserts that Allen discloses the claimed microparticle (liposome) containing an anti-tumor compound with monoclonal antibodies coupled thereto by PEG chains. The rejection further asserts that the monoclonal antibody is specific to a

particular tumor epitope and would therefore have affinity for a non-free target even in the presence of a free target.

In response, Applicants respectfully submit that Allen does not disclose each and every element of the claimed invention, and therefore, the rejection is without appropriate basis and should be withdrawn. In particular, Allen does not disclose the claimed specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. Rather, Allen appears to disclose specificity with respect to tumor epitopes of interest without regard to their status as free or non-free.

The reference in the rejection to "localizing" appears to refer to column 2, lines 32-39 of Allen wherein the liposome PEG coating is discussed. In particular, Allen discloses that the liposomes have selected sizes in the size range 0.05 to 0.12 microns, and contain surface-bound anti-ligand molecules, an anti-tumor compound in liposome-entrapped form, and a surface coating of polyethylene glycol chains, at a surface concentration thereof sufficient to extend the blood circulation time of the liposomes severalfold over that of liposomes in the absence of such coating, thereby to localize the liposomes at the site of the solid tumor.

In fact, it is seen that Allen does not teach or suggest a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand, the ligand having an affinity for a target substance, wherein the affinity allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. For example, according to Applicants' invention, plural numbers of the ligand are bonded to the surface of the mircoparticle, thereby its

apparent affinity is increased. In Applicants' invention, the complex can specifically bind to the non-free target in the presence of both a non-free-target and a free target.

Attention is directed to Allen, at column 2, lines 43-48, wherein it is disclosed that, "The method may also include, following the localization of the antibodies at the site of the solid-tumor, and prior to liposome administration, administration of a multivalent species capable of binding multiple antibodies with attached ligand molecules, to accelerate clearance of such nonspecifically-bound antibodies from the bloodstream." Thus, Allen specifically discloses, prior to liposome administration, administration of a multivalent species to accelerate clearance of nonspecifically-bound antibodies from the bloodstream.

Such use of multivalent species is further disclosed in Allen, at column 12, line 38 et seq. wherein it is disclosed that:

> To minimize nonspecific binding of liposomes containing the liposome-entrapped compound, multivalent species capable of binding multiple antibodies may be administered between about 24 to 48 hours after administration of the biotinylated antibodies to accelerate clearance of the antibodies from the bloodstream. These multivalent species may be empty liposomes having surface-bound avidin, but not containing the liposome-entrapped compound. The empty liposomes may or may not have a hydrophilic polymer surface layer. Alternatively, the multivalent species may be avidin molecules.
>
> These multivalent species serve to chase nonspecifically-bound biotinylated antibodies from sites in the bloodstream. After the chase, liposomes containing the therapeutic compound in liposome-entrapped form, the surface-bound anti-ligand molecules, such as avidin, and the PEG layer on the liposome surface are administered. **Performing the chase with the multivalent species will prevent binding of liposomes containing liposome entrapped-drug at non-specific sites and will maximize the specificity of therapeutic compound targeting in vivo.** (Emphasis added.)

Thus, it is seen that Allen takes specific steps to prevent binding of liposomes containing liposome entrapped-drug at non-specific sites.

The rejection appears to be relying on some type of inherency argument. However, the Examiner is reminded that in order for inherency to be present the Examiner has the burden of showing that the result indicated by the Examiner is the necessary result, and not merely a possible result. In re Oelrich, 212 U.S.P.Q. 323 (CCPA 1981); Ex parte Keith et al., 154 U.S.P.Q. 320 (POBA 1966). The fact that a prior art article may inherently have the characteristics of the claimed product is not sufficient. Ex parte Skinner, 2 U.S.P.Q.2d 1788 (BPAI 1986).

As the Board of Patent Appeals and Interferences states in Ex parte Levy, 17 U.S.P.Q.2d 1461, 1463:

> However, the initial burden of establishing a prima facie basis to deny patentability to a claimed invention rests upon the examiner. In re Piasecki, 745 F.2d 1468, 223 USPQ 785 (Fed. Cir. 1984). In relying upon the theory of inherency, the examiner must provide a basis in fact and/or technical reasoning to reasonably support the determination that the allegedly inherent characteristic necessarily flows from the teachings of the applied prior art. In re King, 801 F.2d 1324, 231 USPQ 136 (Fed. Cir. 1986); W.L. Gore & Associates, Inc. v. Garlock, Inc., 721 F.2d 1540, 220 USPQ 303 (Fed. Cir. 1983); In re Oelrich, 666 F.2d 578, 212 USPQ 323 (CCPA 1981); In re Wilding, 535 F.2d 631, 190 USPQ 59 (CCPA 1976); Hansgirg v. Kemmer, 102 F.2d 212, 40 USPQ 665 (CCPA 1939).

With the above in mind, it is evident that there is no teaching or suggestion in Allen of a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand, the ligand having an affinity for a target substance, wherein the affinity allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. This is especially the case when Allen discloses specific steps to prevent binding of liposomes containing liposome entrapped-drug at non-specific sites.

In view of the above, Applicants respectfully submit that this ground of rejection is without appropriate basis and should be withdrawn.

(b) Claims 1, 4, 9, 13, 16, and 17 are rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent No. 6,156,521 to Buechler et al. ("Buechler"). The rejection asserts that Buechler discloses a ligand (antibody) coupled to a microparticle (signal generating element), which specifically binds to specific regions of a form of troponin or a group of troponins. For example, the rejection asserts Buechler discloses preferential recognition of a ternary troponin complex (said to be a non-free target) in the presence of free troponin I and T (said to be free target).

In response, Applicants respectfully submit that similar arguments concerning inherency apply to this rejection as with respect to the rejection based upon Allen. In this regard, Buechler does not teach or suggest a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand, the ligand having an affinity for a target substance, wherein the affinity allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. As noted above, for example, according to Applicants' invention, plural numbers of the ligand are bonded to the surface of the mircoparticle, thereby its apparent affinity is increased. In Applicants' invention, the complex can specifically bind to the non-free target in the presence of both a non-free target and a free target.

In contrast to Applicants' invention, in the embodiment utilized by the rejection in an attempt to establish inherency merely refers to the use of different antibodies to bind to different components.

Thus, at column 18, line 56 et seq., Buechler discloses that:

> A particularly preferred immunoassay for troponin I involves conjugation of at least two antibodies to a label or a signal generator to form an antibody conjugate. **One of the conjugate antibodies is capable of binding to the troponin T component of the troponin ternary complexes and the other antibody is capable of binding to the free and binary troponin I molecules.** Another antibody or cocktail of antibodies is immobilized on a solid phase, for example, a membrane, and the membrane is placed in a device, as described previously. **The immobilized antibody is complementary with the antibody conjugate antibodies to form sandwich complexes with either troponin I bound to troponin complexes or to the uncomplexed troponin I.** A plasma or serum sample suspected of containing troponin complexes or components from damaged heart muscle is mixed with the antibody conjugate to form a reaction mixture which is allowed to incubate. The reaction mixture is then applied to the aforementioned device. The sample flows through the membrane and the troponin complexes and components, bound to the antibody conjugates, bind to the immobilized antibodies and excess, unbound antibody conjugate is washed away with a wash buffer. The signal is developed and read, either visually or instrumentally. In this assay procedure, **the antibody conjugate binds to the troponin I in ternary complexes through the troponin T specific antibody and all free and binary troponin I molecules through the troponin I specific antibody**. The capture antibody or antibodies on the solid phase bind antibody conjugates that are bound to free troponin I, and to troponin ternary complexes that contain troponin I. (Emphasis added.)

Thus, Buechler relates to a test of a blood sample suspected to contain troponin. There is no disclosure of, e.g., distinguishing a cell-bound target from a free-floating target. Any specificity in Buechler does not relate to free vs. non-free targets, but to troponin and troponin complexes. Also, as is apparent from the paragraph quoted above, Buechler discloses **different antibodies to bind to different materials and does not teach or suggest** a ligand-bonded complex comprising a microparticle directly or indirectly bonded to at least one ligand, the ligand having an affinity for a target substance, wherein the affinity allows specific binding of the complex to a non-free target in the presence of both a non-free target and a free target. Again, as noted above, for example,

according to Applicants' invention, plural numbers of the ligand are bonded to the surface of the mircoparticle, thereby its apparent affinity is increased. In Applicants' invention, the complex can specifically bind to the non-free target in the presence of both a non-free target and a free target. Buechler merely discloses the use of different antibodies.

In view of the above, Applicants respectfully submit that this ground of rejection is without appropriate basis and should be withdrawn.

(c) Claims 2, 3, and 5-8 are rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 6,156,521 to Buechler in view of U.S. Patent No. 5,972,720 to Nichtl et al. ("Nichtl"). The rejection asserts that Nichtl discloses and motivates one skilled in the art to use a water-soluble macromolecule bonded to the microparticle.

In response, Applicants respectfully submit that there is no motivation to combine the disclosures of Buechler and Nichtl. However, for the sake of brevity, arguments in this regard are not being expanded upon herein, because of the deficiencies associated with any combination of the disclosures of these documents. In particular, the above noted deficiencies of Buechler are not in any manner overcome by any disclosure of Nichtl.

Accordingly, this ground of rejection should be withdrawn.

(d) Claim 18 is rejected under 35 U.S.C. § 103(a) as allegedly being obvious over U.S. Patent No. 5,527,528 to Allen in view of U.S. Patent No. 6,294,127 to Lindhofer et al. ("Lindhofer").

The rejection asserts that Allen does not disclose a pharmaceutical composition, but that Lindhofer discloses such and motivates its use in Allen.

In response, Applicants respectfully submit that there is no motivation to combine the disclosures of Allen and Lindhofer. However, for the sake of brevity, arguments in this regard are not being expanded upon herein, because of the deficiencies associated with any combination of the disclosures of these documents. In particular, the above noted deficiencies of Allen are not in any manner overcome by any disclosure of Lindhofer.

Accordingly, this ground of rejection should be withdrawn.

Thus, Applicants respectfully submit that Applicants' claims patentably define their invention, whereby withdrawal of the rejections of record is respectfully requested.

CONCLUSION

In view of the foregoing, the Examiner is respectfully requested to reconsider and withdraw the objections and rejections of record, and allow all the pending claims.

Allowance of the application is requested, with an early mailing of the Notices of Allowance and Allowability.

If the Examiner has any questions or wish to further discuss this application, the Examiner is invited to telephone the undersigned at the below-listed telephone number.

Respectfully submitted,
Toshiaki TAGAWA et al.

Bruce H. Bernstein
Reg. No. 29,027

Reg. No. 33,094

June 16, 2003
GREENBLUM & BERNSTEIN, P.L.C.
1950 Roland Clarke Place
Reston, VA 20191
(703) 716-1191

APPENDIX

MARKED UP COPY OF AMENDED CLAIM 9

9. (Twice Amended) The ligand-bonded complex according to claim 1, wherein the microparticle is selected from the group consisting of a low molecular drug, [a marker molecule,] a protein, a micelle, and a liposome.